

AMENDMENTS TO THE CLAIMS:

Please incorporate the following amendments into the claims of the subject application.

1-33. (canceled)

34. (previously presented) The method of claim 69 wherein the compound is determined to be a compound that reduces the activity of an active receptor state of said constitutively activated GPCR.

35-39. (canceled)

40. (previously presented) The method of claim 70 wherein the compound is determined to be a compound that reduces the activity of an active receptor state of said constitutively active GPCR.

41-44. (canceled)

45. (previously amended) The method of claim 69 wherein the third intracellular loop of the endogenous GPCR of step (a) comprises the following sequence:

X1BBHyX2

wherein X1 is an amino acid; B is a basic amino acid; Hy is a hydrophobic amino acid; and X2 is an amino acid.

46. (original) The method of claim 45 wherein X1 is glycine.

47. (original) The method of claim 45 wherein X1 is lysine.

48. (original) The method of claim 45 wherein Hy is alanine.

49. (original) The method of claim 45 wherein X2 is lysine.

50. (original) The method of claim 45 wherein X2 is arginine.

51. (original) The method of claim 45 wherein X2 is glutamic acid.

52. (previously presented) The method of claim 69 wherein the second intracellular loop of the endogenous GPCR of step (a) comprises the following sequence:

XRY

wherein X can be any amino acid other than aspartic acid; R is arginine; and Y is tyrosine.

53. (previously presented) The method of claim 70 wherein the third intracellular loop of the constitutively active GPCR of step (a) comprises the following sequence:

X1BBHyX2

wherein X1 is an amino acid; B is a basic amino acid; Hy is a hydrophobic amino acid; and X2 is an amino acid.

54. (original) The method of claim 53 wherein X1 is glycine.

55. (original) The method of claim 53 wherein X1 is lysine.

56. (original) The method of claim 53 wherein Hy is alanine.

57. (original) The method of claim 53 wherein X2 is lysine.

58. (original) The method of claim 53 wherein X2 is arginine.

59. **(currently amended)** The method of claim 53 wherein X2 is ~~glutamic~~ **glutamic** acid.

60. (previously presented) The method of claim 70 wherein the second intracellular loop of the constitutively active GPCR of step (a) comprises the following sequence:

XRY

wherein X can be any amino acid other than aspartic acid; R is arginine; and Y is tyrosine.

61. (original) The method of claim 45 wherein the sequence XIBBH<sub>y</sub>X<sub>2</sub> is an endogenous sequence.

62. (original) The method of claim 52 wherein the sequence XRY is an endogenous sequence.

63. (previously amended) The method of claim 69 wherein said mammal is a human.

64. (previously amended) The method of claim 70 wherein said mammal is a human.

65. (previously amended) The method of claim 69 wherein said mammal is a non-human mammal.

66. (previously amended) The method of claim 70 wherein said mammal is a non-human mammal.

67.-68. (canceled)

69. (previously amended) A method for directly identifying a non-endogenous candidate compound as a compound that stimulates an endogenous G protein coupled receptor (GPCR) or reduces the activity of an active receptor state of an endogenous GPCR, wherein said endogenous GPCR has been associated with a disease or disorder in a mammal and wherein an endogenous ligand for said endogenous GPCR has not been identified, said method comprising the steps of:

(a) subjecting said endogenous GPCR to constitutive receptor activation to create a constitutively activated GPCR;

(b) contacting the non-endogenous candidate compound with said constitutively activated GPCR;

(c) determining whether said non-endogenous candidate compound is a compound that stimulates said endogenous GPCR or reduces the activity of an active receptor state of said endogenous GPCR, by measuring the ability of the compound to stimulate or inhibit functionality of said constitutively activated GPCR, respectively.

70. (previously amended) A method for directly identifying a non-endogenous candidate compound as a compound that stimulates an endogenous constitutively active G protein coupled receptor (GPCR) or reduces the activity of an active receptor state of an endogenous constitutively active GPCR, wherein said endogenous GPCR has been associated with a disease or disorder in a mammal and wherein an endogenous ligand for said constitutively active GPCR has not been identified, said method comprising the steps of:

- (a) contacting the non-endogenous candidate compound with said constitutively active GPCR;
- (b) determining by measurement of the ability of the compound to inhibit or stimulate functionality of said constitutively active GPCR, whether said non-endogenous candidate compound is a compound that stimulates said constitutively activate GPCR or reduces the activity of an active receptor state of said constitutively activate GPCR.

71. (withdrawn) A compound directly identified by the method of claim 69.

72. (withdrawn) A compound directly identified by the method of claim 70.

73. (withdrawn) A pharmaceutical composition comprising the compound of claim 71.

74. (withdrawn) A pharmaceutical composition comprising the compound of claim 72.

75.–76. (canceled)

Please add the following claims:

77. **(New)** A method for directly identifying a non-endogenous candidate compound with compound efficacy as to an endogenous orphan GPCR, the method comprising the steps of:

- (a) subjecting said endogenous orphan GPCR to constitutive receptor activation to create a constitutively activated orphan GPCR;
- (b) contacting the constitutively activated orphan GPCR with the non-endogenous compound;

(c) comparing the functionality of the constitutively activated orphan GPCR in the presence and absence of the non-endogenous compound; and

(d) identifying the non-endogenous compound as having compound efficacy if the presence of the compound measurably alters the functionality of the endogenous constitutively activated orphan GPCR as compared to the functionality of the endogenous constitutively activated orphan GPCR in the absence of the compound.

78. **(New)** A method for directly identifying a non-endogenous candidate compound with compound efficacy as to an endogenous constitutively activated orphan GPCR, the method comprising the steps of:

(a) contacting the constitutively activated orphan GPCR with the non-endogenous compound;

(b) comparing the functionality of the constitutively activated orphan GPCR in the presence and absence of the non-endogenous compound; and

(c) identifying the non-endogenous compound as having compound efficacy if the presence of the compound measurably alters the functionality of the endogenous constitutively activated orphan GPCR as compared to the functionality of the endogenous constitutively activated orphan GPCR in the absence of the compound.

79. **(New)** The method of claim 77 or 78, wherein said functionality of the constitutively activated orphan GPCR is binding to GTP.